



Risk factors and 90-day mortality after video-assisted thoracoscopic lobectomy for lung cancer: the discussion is still open

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American College of Chest Physician (ACCP) promotes the use of video-assisted thoracoscopic procedure over thoracotomy for patients with stage I NSCLC for anatomical pulmonary resection in experienced centers (1). Video-assisted thoracoscopic surgery (VATS) lobectomy has been demonstrated to be a safe, minimally invasive approach for the surgical treatment of lung cancer. Minimally invasive surgery seems to reduce postoperative morbidity and early mortality. For this reason it is currently the recommended surgical approach for early stage lung cancer surgical patients. But which are the real risk factors for vats lobectomy? And is thirty-day mortality an adequate quality indicator?

A variety of patient-dependent variables have been associated with an elevated risk of perioperative complications after lung resection, with evidences derived from institutional studies as well as larger repositories, such as The Society of Thoracic Surgeons (STS) General Thoracic Database (GTDB). These variables include gender, preoperative forced expiratory volume in 1 second (FEV1), preoperative diffusing capacity of the lung for carbon monoxide (DLCO), poor performance status, obesity, renal disease, diabetes, malnutrition, steroid use and congestive heart failure (2). Other factors that can influence the optimal result are operative time and high volume centers (mio6). Furthermore low mortality was correlated with higher surgeon volume (3). However, by reviewing the literature, there is a discrepancy in terms of which factors have the highest impact on results. Some authors recognize only a few of the above factors and not others. This is probably due to the different sampling used for the study, whether it is mono- or multi-centric, the cut-offs established and the

expected target (mortality, prolonged stay, complications, patient's satisfaction...).

Postoperative mortality is the most commonly reported measure of surgical quality, however there is an ongoing debate on which is the most representative timepoint (30 or 90 days). In general the VATS approach has been associated with short hospital stay and a greater proportion of patients are then discharged after a few days. The complications could occur at home and patients could die there, leading to underreporting of surgically related deaths. In-hospital or 30-day mortality rates could be artificially underestimated and may represent misleading information. So a longer period of observation could provide a more accurate measure of mortality. Several reports have in fact shown that the 90-day mortality rate doubled the 30-day mortality rate (4-9). However, none of those studies has been focusing specifically on VATS patients.

Brunelli's recent article combines these two issues: he evaluated the incidence and risk factors of 90-day mortality rate after VATS lobectomy (10). This article showed that factors significantly associated with 90-day mortality were male sex ($P=0.001$), DLCO less than 60% ($P=0.001$), and operative time longer than 150 minutes ($P=0.03$).

All three risk factors have correspondence in literature, even if not all authors identify DLCO as a better marker, some find FEV1 as a major risk factor. The American College of Surgery Oncology Group (ACOSOG) trials z4032 and z4033 prospectively characterized lung cancer patients as "high-risk" for surgical intervention, and these results are frequently reported in the literature (2). In 2014 Puri *et al.* show that a significant portion of patients considered as "high-

risk” by national cooperative group trials (mentioned above) safely undergo lobectomy (2), and this study was including open and VATS resection. Furthermore Berry *et al.* (11) affirm that in patients with impaired pulmonary function, preoperative pulmonary function tests are predictors of pulmonary complications only in open lobectomy but not in thoracoscopic. It is also known that for patients with reduced functional capacity the execution of VATS lobectomy *vs.* open can provide particular benefit.

The duration of surgery is directly related to its complexity, which *per se* can increase postoperative risk. One of the major causes of prolonged surgery is the presence of pleural adherence; patients undergoing major lung resection who have pleural adhesions have an increased incidence of adverse surgical outcomes and higher pleural morbidity (12). However, there are other pathophysiologic factors associated with prolonged surgical time that can influence the postoperative course. Prolonged duration of anesthesia and surgery can lead to long periods of hypotension, fluid imbalance, hypothermia, and “surgical shock” leading to variable degrees of oxygen debt (13). In lung surgeries the effect of protracted one lung ventilation can negatively affect both the ventilated and the non-ventilated lungs through several mechanisms (14) among which hypoperfusion/ischemia-reperfusion injury caused by hypoxic pulmonary vasoconstriction.

The duration of the surgery depends not only on technical difficulties but also on the ability and experience of the surgeon. It is not possible, however, to predict in advance whether the surgical period will be prolonged, remains to be defined when and if it is necessary to perform a conversion to thoracotomy if the operating time becomes too long. It is not clear yet whether prolonged operating time or thoracotomy (not in emergency) is more important as a risk factor. The 3D system seems to require a shorter surgery (15) and together with the improvement of the technologies could lead to a general decrease in surgical time.

Brunelli and colleagues found in their series that 90-day mortality was not much higher than 30-day mortality after VATS lobectomy. In hospital/30-day mortality rate was 1.9%. The conditional 90-day mortality rate (deaths occurred between 30 and 90 days after the operation) was only 0.6% and the total 90-day mortality rate was 2.5%. This finding differs from what has been generally reported in literature. Several reports have in fact shown that the 90-day mortality rate doubled the 30-day mortality rate (4-9) but these papers don't distinguish VATS from open lobectomies.

The Brunelli's results are similar to the ones reported in a publication from the Danish Lung Cancer Registry (16): in lobectomy patients (open and VATS), the study found a 90-day mortality rate of 2.1% (only 0.4% higher than their 30-day mortality rate). Could this be due to the high percentage of VATS lobectomy in Denmark? Is this enough to say that VATS lobectomy does not lead to a 90-day mortality risk increase? Another bias may be due to the fact that open lobectomies are also performed in more advanced stages: it is not only the technique but also the stage of disease that is important in 90-day mortality. In fact most candidates for VATS lobectomy have early-stage lung cancer, which reduces the presence of other confounding factors associated with mortality after discharge, such as cancer progression or complications from adjuvant treatment. Brunelli's study is a one-centered study, in Leeds they performed about 200 VATS lobectomies each year, it is then a high volume center: would the results be the same if we would associate low and high volume centers, as in multicenter studies or on national databases based studies? The volume outcome relationship has been used as proxy measure for almost 4 decades since first proposed by Luft and colleagues in 1979 (17). It is now well known that patients undergoing VATS by high-volume surgeons have reduced postoperative complications and improved survival. The same Brunelli in his article, having found the surgical time as a risk factor, suggests that high risk patients (males and with reduced DLCO) should be operated by the most experienced surgeon in the unit.

In conclusion, the decreased surgical trauma with VATS is particularly beneficial to patients considered at high risk for surgery. In particular in this era of patient share decision making, a more accurate understanding of risk factors of VATS lobectomy is key to have a proper multidisciplinary discussion and choose the best treatment (10). However, a real definition of “high-risk” remains a critical unmet need in patient care submitted to VATS lobectomy. Thirty or 90-day mortality seems to show no significant differences in VATS lobectomy patients, but there are no multicenter studies to define it without any doubts.

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